EXHIBIT S

JAMA Internal Medicine | Original Investigation

Pharmaceutical Industry–Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries

Colette DeJong, BA; Thomas Aguilar, MS; Chien-Wen Tseng, MD, MPH; Grace A. Lin, MD, MAS; W. John Boscardin, PhD; R. Adams Dudley, MD, MBA

IMPORTANCE The association between industry payments to physicians and prescribing rates of the brand-name medications that are being promoted is controversial. In the United States, industry payment data and Medicare prescribing records recently became publicly available.

OBJECTIVE To study the association between physicians' receipt of industry-sponsored meals, which account for roughly 80% of the total number of industry payments, and rates of prescribing the promoted drug to Medicare beneficiaries.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional analysis of industry payment data from the federal Open Payments Program for August 1 through December 31, 2013, and prescribing data for individual physicians from Medicare Part D, for all of 2013. Participants were physicians who wrote Medicare prescriptions in any of 4 drug classes: statins, cardioselective β-blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (ACE inhibitors and ARBs), and selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs). We identified physicians who received industry-sponsored meals promoting the most-prescribed brand-name drug in each class (rosuvastatin, nebivolol, olmesartan, and desvenlafaxine, respectively). Data analysis was performed from August 20, 2015, to December 15, 2015.

EXPOSURES Receipt of an industry-sponsored meal promoting the drug of interest.

MAIN OUTCOMES AND MEASURES Prescribing rates of promoted drugs compared with alternatives in the same class, after adjustment for physician prescribing volume, demographic characteristics, specialty, and practice setting.

RESULTS A total of 279 669 physicians received 63 524 payments associated with the 4 target drugs. Ninety-five percent of payments were meals, with a mean value of less than $20. Rosuvastatin represented 8.8% (SD, 9.9%) of statin prescriptions; nebivolol represented 3.3% (7.4%) of cardioselective β-blocker prescriptions; olmesartan represented 1.6% (3 9%) of ACE inhibitor and ARB prescriptions; and desvenlafaxine represented 0.6% (2.6%) of SSRI and SNRI prescriptions. Physicians who received a single meal promoting the drug of interest had higher rates of prescribing rosuvastatin over other statins (odds ratio [OR], 1.18; 95% CI, 1.17-1.18), nebivolol over other β-blockers (OR, 1.70; 95% CI, 1.69-1.72), olmesartan over other ACE inhibitors and ARBs (OR, 1.52; 95% CI, 1.51-1.53), and desvenlafaxine over other SSRIs and SNRIs (OR, 2.18; 95% CI, 2.13-2.23). Receipt of additional meals and receipt of meals costing more than $20 were associated with higher relative prescribing rates.

CONCLUSIONS AND RELEVANCE Receipt of industry-sponsored meals was associated with an increased rate of prescribing the brand-name medication that was being promoted. The findings represent an association, not a cause-and-effect relationship.

Editor's Note page 1123

Supplemental content at jamainternalmedicine.com

CME Quiz at jamanetworkcme.com and CME Questions page 1240

Author Affiliations: Center for Healthcare Value, Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco School of Medicine (DeJong, Aguilar, Lin, Dudley); Department of Family Medicine and Community Health, University of Hawaii John A. Burns School of Medicine, Honolulu (Tseng); Pacific Health Research and Education Institute, Honolulu, Hawaii (Tseng); Department of Medicine, University of California, San Francisco School of Medicine (Lin, Dudley); Department of Medicine and Department of Epidemiology and Biostatistics, University of California, San Francisco School of Medicine (Boscardin).

Corresponding Author: R. Adams Dudley, MD, MBA, Center for Healthcare Value, Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco, PO Box 0936, 3333 California, Ste 265, San Francisco, CA 94118 (Adams.Dudley@ucsf.edu).

JAMA Intern Med. 2016;176(8):1114-1122. doi:10.1001/jamainternmed.2016.2765
Published online June 20, 2016. Corrected on August 1, 2016.

Physician-industry relationships—including sponsored meals and promotional speaking fees—are at the center of an international debate, intensified by recent transparency efforts in the United States and the European Union.[1-5] In the United States, in the last 5 months of 2013, 4.3 million industry payments totaling $3.4 billion were made to more than 470 000 physicians and 1000 teaching hospitals.[1] Although some argue that industry-sponsored meals and payments facilitate the discussion of novel treatments,[6,7] others have raised concerns about their potential to influence prescribing behavior.[8,9]

Studies suggest that physician-industry relationships are associated with increased prescribing of brand-name drugs. Although most studies have relied on physician surveys[10-13] or regional data,[14,15] recent analyses of physician-specific payment records found a positive association between physicians' receipt of industry payments and the total percentage of their Medicare Part D prescriptions that are written for brand-name drugs.[4,16,17] These analyses, however, did not identify the specific drug being promoted by each payment or assess the link between promotion and prescribing of individual drugs. In one study, the association between payments and prescribing was only significant among physicians who received at least $2000 from industry.[16] It is not known whether much smaller payments, such as sponsored meals, are associated with increased prescribing of the promoted brand-name drug over therapeutic alternatives.

We linked physician data sets from the Open Payments program and Medicare Part D to examine the association between industry payments and prescribing rates of the brand-name medications that were being promoted. We focused on meals sponsored by the pharmaceutical industry, which constitute nearly 80% of the total number of payments by drug and device manufacturers to physicians.[1]

Key Points

Question Is the receipt of pharmaceutical industry-sponsored meals by physicians associated with their prescribing the promoted brand-name drug at higher rates to Medicare beneficiaries?

Findings In this cross-sectional study of 279 669 physicians, physicians who received a single meal promoting the drug of interest, with a mean value of less than $20, had significantly higher rates of prescribing rosuvastatin as compared with other statins; nebivolol as compared with other β-blockers; olmesartan as compared with other angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers; and desvenlafaxine as compared with other selective serotonin and serotonin-norepinephrine reuptake inhibitors.

Meaning Receipt of industry-sponsored meals was associated with an increased rate of prescribing the promoted brand-name medication to Medicare patients.

Methods

Study Population

This study was approved by the institutional review board at the University of California, San Francisco. We identified physicians who appeared in both Physician Compare[18] and the 2013 Medicare Part D Prescriber file,[19] which reports an end-of-year count of each physician's filled prescriptions. We excluded physicians whose total number of brand-name prescriptions was redacted because of low claim count. From this population, we created 4 study groups, each containing physicians who wrote more than 20 filled prescriptions in 1 of 4 drug categories: 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), cardioselective β-blockers without sympathomimetic activity, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACE inhibitors and ARBs), and selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs). These classes are first-line treatments for common conditions and have been included in previous studies of prescribing of brand-name drugs.[20,21] Individual physicians could be included in more than 1 study group (eTable 1 and eFigure in the Supplement).

Drugs prescribed 10 or fewer times in a calendar year are not reported in that physician's Medicare prescribing record; to ensure that this redaction—which may affect our analysis of low-volume prescribers—did not significantly affect our results, we conducted a sensitivity analysis in which we increased our study group inclusion threshold from 20 to 200 prescriptions in the class.

Selection of Target Drugs

We identified the most-prescribed brand-name drug in each of the 4 drug categories in Medicare Part D in 2013. We required that each drug be patent protected through December 2014 and therefore not subject to pharmacy-level automatic substitution laws[22] or declining promotion by the manufacturer in the last year of patent protection.[23] The resulting target drugs were rosuvastatin calcium (Crestor; AstraZeneca) among statins, nebivolol (Bystolic; Forest Laboratories) among cardioselective β-blockers, olmesartan medoxomil (Benicar; Daiichi Sankyo) among ACE inhibitors and ARBs, and desvenlafaxine succinate (Pristiq; Pfizer) among SSRIs and SNRIs.

The US Food and Drug Administration (FDA) approved all 4 target drugs 5 to 11 years before the study period, and all have generic alternatives in their class.[24] There is limited, mixed, or contrary evidence about the superiority of these 4 drugs over generic alternatives,[25-28] and all 4 are excluded from the national formulary for the US Department of Veterans Affairs medical sytem.[29]

Measures of Industry Payments

The 2013 Open Payments database describes the value and the drug or device being promoted for all payments to physicians from August through December 2013, as reported by pharmaceutical companies. Of the records, 95% identify a specific drug or device. Group payments, such as sponsored meals, are divided in value among the physicians present; when it is impossible to identify recipients (such as when refreshments are offered to all attendees of an annual conference), the payment is exempt from reporting. Because the first release of Open Payments data included records that were disputed during the phy-

sician review process, we examined data from the second release and excluded any remaining disputed payments.

We identified all target payments—defined as those promoting 1 of the 4 target drugs—made to physicians in the study groups. We included payments promoting multiple products. We used physician name and location to link each physician's payments with his or her prescription records, and excluded physicians with identical matching criteria to avoid inadvertently matching 1 physician's prescribing records with another physician's payment records.

The exposure of interest was industry-sponsored meals. Because meals were often reported as multiple small food payments on the same day, our primary measure of industry contact was number of days receiving a meal related to the promotion of a target drug during the 5-month study period. We limited our regression analysis to the 91% to 99% of physicians in each group whose only payments related to target drugs were for meals, excluding those who received other types of payment, such as research grants, consulting, and royalties.

Measures of Prescribing

For each physician, relative rates of prescribing a target drug were calculated as a percentage of that physician's total Medicare Part D prescriptions in the drug category in 2013. Our primary analysis did not standardize prescriptions by quantity of medications supplied; we conducted a sensitivity analysis in which we standardized claims to 30-day supplies.

Covariates

We adjusted for each physician's specialty; sex; region; practice size; number of years since medical school graduation; rural or urban practice setting[30]; median household income in zip code according to 2000 US Census data[31]; prescribing volume within the drug class of interest in Medicare Part D; overall rate of brand-name drug prescribing across all drug classes in Medicare Part D; and percentage of prescriptions written for low-income subsidy beneficiaries, who have limited cost sharing for brand-name drugs, and Medicare Advantage beneficiaries, who obtain prescriptions through a managed care model with associated formulary differences.

Statistical Analysis

First, using χ^2 tests for categorical variables and 2-sample *t* tests for continuous variables, we tested the association between the aforementioned covariates and receipt of industry payments. We then compared mean rates of target-drug prescribing among physicians who received meals related to target drugs on 0 to 4 or more days during the study period. We used Cochrane-Armitage trend tests to assess trends in prescribing behavior between groups.

Next, using multivariable grouped logistic regression models with binomial physician-level prescribing data, and adjusting for the aforementioned covariates, we measured the association between the number of days that a physician received meals related to target drugs and his or her prescribing rate of the promoted drug as a proportion of prescriptions in the class.

To examine the relationship between cost per meal and prescribing patterns, we first restricted our regression analysis to physicians who received at least 1 meal and adjusted for the mean cost per meal received by each prescriber (<$20 or ≥$20). Next, in effect modifier analyses, we assessed whether the association between number of days receiving a meal and prescribing of a target drug was affected by mean cost per meal.

We conducted a sensitivity analysis using propensity score matching. We created a dichotomous outcome variable indicating whether a physician received any target meals; calculated individual propensity scores using grouped logistic regression models, with the baseline characteristics in **Table 1** included as predictor variables; and reran our main regression analysis while controlling for the decile of propensity score.

To isolate the association between prescribing and promotion of a specific drug, rather than general exposure to industry promotion, we conducted a falsification test. Using the aforementioned regression methods, we assessed whether receipt of meals targeting rosuvastatin predicted desvenlafaxine prescribing among physicians who received no desvenlafaxine payments, and vice versa.

We performed a sensitivity analysis on rosuvastatin, which is 1 of the 2 high-intensity statins (rosuvastatin and atorvastatin calcium) that are available in the United States and recommended in clinical guidelines for patients with clinical atherosclerotic cardiovascular disease or severe hyperlipidemia.[32] To reduce the potential impact of case mix on our results, we recalculated relative prescribing rates of rosuvastatin as a percentage of filled claims for only rosuvastatin or atorvastatin, and reran the multivariable regression analysis.

All *P* values were 2-tailed, and $P \leq .05$ was considered significant. Analyses were conducted using R, version 3.1.2 (R Foundation for Statistical Computing), and SAS software, version 9.4 (SAS Institute).

Results

The study population included 279 669 physicians (eFigure in the Supplement). Of these, 155 849 physicians wrote more than 20 prescriptions in 1 of the 4 target drug classes and were assigned to study groups. Characteristics of the 4 study groups are presented in Table 1. A total of 129 675 (83%) of the sample physicians were assigned to multiple study groups, and 88 724 (57%) were included in all 4 groups.

Across the 4 study groups, 2% to 12% of physicians received payments promoting the target drug (**Table 2**). Of 63 524 payments (total value of $1.4 million) related to target drugs, 95% were for sponsored meals, with a mean value of $12 to $18 per meal. The remaining 5% of payments promoting the target drugs included speaking fees, honoraria, travel expenses, and education (such as providing free textbooks or journal articles); physicians receiving these nonmeal payments were excluded from the regression analysis. Rosuvastatin represented 8.8% (SD, 9.9%) of statin prescriptions; nebivolol represented 3.3% (7.4%) of cardioselective β-blocker prescriptions; olmesartan represented 1.6% (3.9%) of ACE inhibitor and ARB prescriptions; and desvenlafaxine represented 0.6% (2.6%) of SSRI and SNRI prescriptions. Physicians who received meals related to target drugs had a

Table 1. Characteristics of Sample Physicians According to Study Group[a]

Characteristic	Statin Prescribers (n = 131 207)	β-Blocker Prescribers (n = 126 134)	ACE Inhibitor and ARB Prescribers (n = 131 343)	SSRI and SNRI Prescribers (n = 123 318)
Demographic				
Male sex, %	91 699 (70)	89 541 (71)	91 883 (70)	85 182 (69)
Specialty, %				
Internal medicine	47 844 (36)	46 780 (37)	48 046 (37)	42 107 (34)
Family medicine and general practice	56 460 (43)	54 346 (43)	56 503 (43)	51 173 (42)
Cardiology	12 152 (9)	13 070 (10)	12 495 (10)	NA
Psychiatry	NA	NA	NA	12 680 (10)
Other	14 751 (11)	11 938 (9)	14 299 (11)	17 358 (14)
Group practice size, %				
1	29 345 (22)	28 178 (22)	29 170 (22)	30 062 (24)
2-10	26 466 (20)	25 501 (20)	26 555 (20)	25 820 (21)
11-50	20 304 (15)	19 643 (16)	20 486 (16)	19 454 (16)
≥51	55 092 (42)	52 812 (42)	55 132 (42)	47 982 (39)
Years since medical school graduation, %				
0-5	4484 (3)	3678 (3)	4610 (4)	3290 (3)
6-20	49 449 (38)	47 443 (38)	49 785 (38)	44 952 (36)
≥21	77 274 (59)	75 013 (59)	76 948 (59)	75 076 (61)
US geographic region, %				
Northeast	27 355 (21)	26 212 (21)	27 086 (21)	25 255 (20)
Midwest	31 192 (24)	30 345 (24)	31 350 (24)	29 770 (24)
South	44 543 (34)	42 891 (34)	44 686 (34)	42 573 (35)
Pacific West	18 749 (14)	17 884 (14)	18 732 (14)	17 291 (14)
Mountain West	7162 (5)	6744 (5)	7283 (6)	6760 (5)
Urban location, %	106 783 (81)	102 157 (81)	106 810 (81)	99 499 (81)
Median household income in zip code, mean (SD), $1000	44.1 (17.6)	44.0 (17.4)	44.0 (17.6)	44.4 (17.5)
% claims for low-income subsidy beneficiaries, mean (SD)	42.3 (26.0)	41.9 (25.8)	42.5 (26.0)	44.9 (26.3)
% claims for Medicare Advantage Part D beneficiaries, mean (SD)	33.2 (24.8)	33.4 (24.9)	33.2 (24.8)	32.1 (24.5)
Prescribing				
Proportion of all 2013 claims (in any drug class) written for branded drugs, mean (SD)	23.0	22.4	22.9	21.8
Total claims within the drug class of interest (per MD), mean (SD)	514 (461)	303 (277)	407 (370)	272 (314)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NA, not applicable; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Study groups include physicians from the study population who prescribed more than 20 filled claims within the drug category in 2013. Percentages do not add up to 100% owing to missing observations.

greater mean prescribing volume than those who did not (742.2 vs 470.1 statin prescriptions, 410.0 vs 299.8 β-blocker prescriptions, 562.7 vs 394.8 ACE inhibitor and ARB prescriptions, and 437.6 vs 269.5 SSRI and SNRI prescriptions; all comparisons, $P < .001$).

Characteristics of the larger study population, divided between physicians who did and did not receive industry payments of any kind (not limited to the 4 target drugs), are shown in eTable 2 in the Supplement. Compared with physicians receiving no payments, higher proportions of those receiving payments were men (110 143 [76%] vs 90 651 [67%]), solo practitioners (32 028 [22%] vs 24 233 [18%]), and practiced in the South (56 828 [40%] vs 38 335 [29%]). Physicians receiving payments wrote fewer claims for low-income subsidy beneficiaries (40% vs 43%) and Medicare Advantage beneficiaries (30% vs 33%). All characteristics were significantly associated with receipt of payment (all comparisons, $P < .001$).

Unadjusted Analyses

Figure 1 shows relative rates of target-drug prescribing as a function of days receiving meals related to target drugs. Physicians receiving meals related to target drugs on 4 or more days prescribed rosuvastatin at 1.8 times the rate (15.2% vs 8.3%), nebivolol at 5.4 times the rate (16.7% vs 3.1%), olmesartan at 4.5 times the rate (6.3% vs 1.4%), and desvenlafaxine at 3.4 times the rate (1.7% vs 0.5%) of physicians receiving no target meals (all comparisons, $P < .001$). All tests of trend were significant ($P < .001$).

Adjusted Analyses

In multivariable logistic regression models (Table 3), sponsored meals were associated with increased target-drug prescribing in each class ($P < .001$). Physicians receiving a single meal promoting the drug of interest were more likely to prescribe rosuvastatin over other statins (adjusted odds ratio [OR],

Table 2. Characteristics of Target-Drug–Specific Payments[a] to Physicians in Each Study Group

Characteristics of Target-Drug–Specific Payments[a]	Statin Prescribers (n = 131 207)	β-Blocker Prescribers (n = 126 134)	ACE Inhibitor and ARB Prescribers (n = 131 343)	SSRI and SNRI Prescribers (n = 123 318)
Physicians receiving payments, No. (%)	15 941 (12)	3843 (3)	9483 (7)	1926 (2)
Total value of target-drug-specific payments, $	915 728	194 052	284 335	35 382
Value of payments per physician, mean (SD), $	58 (1075)	51 (256)	30 (61)	18 (75)
Maximum value of payments per physician, $	62 530	4192	3815	3200
Distribution of payments, No. (%)				
Food and beverages	29 639 (99)	5001 (66)	22 858 (>99)	3012 (>99)
Education	37 (<1)	2419 (32)	81 (<1)	0 (0)
Other[b]	322 (1)	146 (2)	8 (<1)	1 (<1)
Mean value per payment, mean (SD), $				
Sponsored meal[c]	18 (15)	13 (13)	14 (5)	12 (6)
Education	7 (5)	3 (8)	1 (1)	0
Other	1400 (7194)	850 (781)	1173 (1315)	3200[d]
Days receiving sponsored meals for the target drug of physicians, No. (%)[e]				
0	115 275 (88)	122 702 (97)	121 874 (93)	121 393 (98)
1	9708 (7)	2571 (2)	5380 (4)	1366 (1)
2	3689 (3)	570 (<1)	1955 (1)	368 (<1)
3	1587 (1)	193 (<1)	799 (1)	99 (<1)
≥4	948 (1)	98 (<1)	1335 (1)	92 (<1)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] The target drugs were rosuvastatin (Crestor) in the statin study group, nebivolol (Bystolic) in the β-blocker study group, olmesartan (Benicar) in the ACE inhibitor and ARB study group, and desvenlafaxine succinate (Pristiq) in the SSRI and SNRI study group.

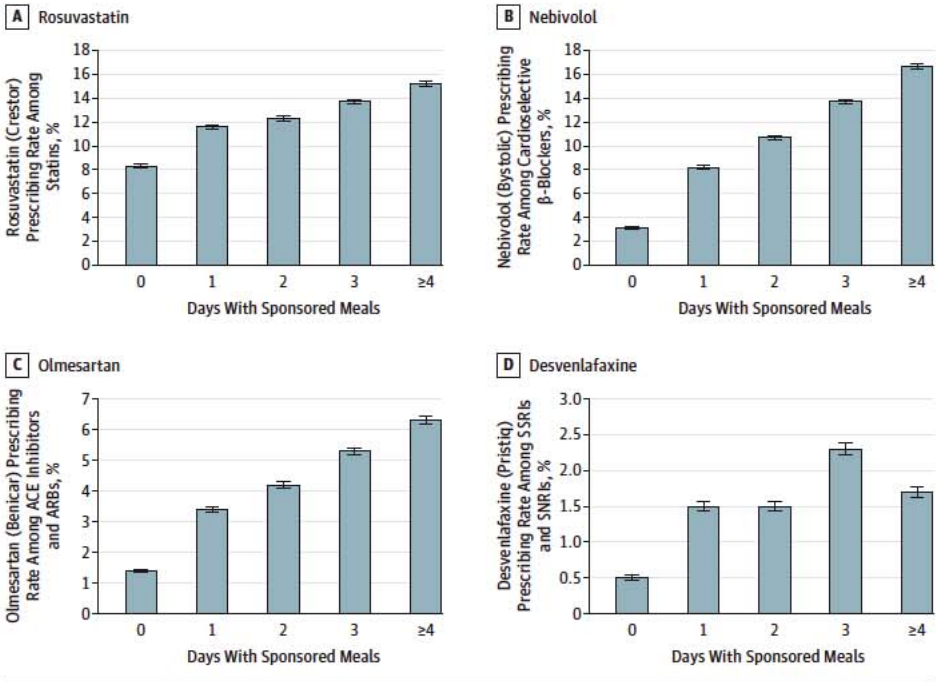
[b] Other includes gifts, entertainment, travel and lodging, consulting fees, speaking fees and honoraria, charitable contributions, and space rental or facility fees.

[c] Refers to the primary exposure of interest, that is, the sum of all food and beverage payments received by a physician in 1 day.

[d] Because this refers to a single payment, there is no standard deviation.

[e] Refers to the number of days between August 1 and December 31, 2013, in which the physician received at least 1 food or beverage payment promoting the target drug.

Figure 1. Target Branded Drugs as a Percentage of All Filled Prescriptions in the Class in 2013, Across Days Receiving Target Drug–Sponsored Meals



Filled prescriptions for each target branded drug are shown as a percentage of all prescriptions within the class, according to number of days receiving target drug-sponsored meals. A, Statins. B, Cardioselective β-blockers. C, Angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers (ACE inhibitors and ARBs). D, Selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs). Sample sizes for Figure 1 are shown in the last 5 rows of Table 2. Error bars indicate 95% confidence intervals.

1.18; 95% CI, 1.17-1.18), nebivolol over other β-blockers (OR, 1.70; 95% CI, 1.69-1.72), olmesartan over other ACE inhibitors and ARBs (OR, 1.52; 95% CI, 1.51-1.53), and desvenlafaxine over other SSRIs and SNRIs (OR, 2.18; 95% CI, 2.13-2.23). Additional meals were associated with greater increases in relative prescribing rates ($P < .001$).

Table 3. Predictors of Target Drug Prescribing[a]

Variable	Odds Ratio (95% CI)			
	Rosuvastatin (n = 111 588)	Nebivolol (n = 116 356)	Olmesartan (n = 121 319)	Desvenlafaxine (n = 113 984))
Days receiving target-drug-sponsored meals[b]				
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1	1.18 (1.17-1.18)	1.70 (1.69-1.72)	1.52 (1.51-1.53)	2.18 (2.13-2.23)
2	1.19 (1.19-1.20)	1.87 (1.84-1.90)	1.79 (1.77-1.81)	2.34 (2.25-2.44)
3	1.24 (1.23-1.25)	2.18 (2.13-2.24)	1.98 (1.96-2.01)	3.21 (3.03-3.41)
≥4	1.34 (1.33-1.35)	2.42 (2.34-2.51)	2.26 (2.23-2.28)	2.47 (2.32-2.63)
Sex				
Male	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Female	1.05 (1.05-1.05)	0.88 (0.88-0.89)	1.05 (1.04-1.06)	0.83 (0.83-0.84)
Total volume of claims within the drug class[c]	1.01 (1.01-1.01)	1.01 (1.01-1.01)	1.03 (1.02-1.03)	1.00 (1.00-1.00)
Specialty				
Internal medicine	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Family medicine and general practice	1.03 (1.03-1.03)	1.07 (1.07-1.07)	0.97 (0.96-0.97)	1.14 (1.13-1.16)
Cardiology	1.64 (1.64-1.65)	1.27 (1.26-1.28)	0.94 (0.93-0.94)	NA
Psychiatry	NA	NA	NA	6.59 (6.51-6.67)
Other	0.93 (0.92-0.93)	0.93 (0.93-0.94)	0.72 (0.72-0.73)	1.08 (1.06-1.10)
No. of members in group practice				
1	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
2-10	0.92 (0.91-0.92)	0.94 (0.94-0.95)	0.87 (0.86-0.87)	0.90 (0.89-0.91)
11-50	0.92 (0.91-0.92)	0.86 (0.85-0.86)	0.83 (0.82-0.83)	0.86 (0.85-0.87)
≥51	0.92 (0.92-0.92)	0.72 (0.72-0.73)	0.78 (0.77-0.78)	0.71 (0.70-0.72)
% of prescriptions for branded drugs				
<25th percentile	0.68 (0.67-0.68)	0.45 (0.45-0.45)	0.53 (0.53-0.54)	0.49 (0.48-0.49)
25th-75th percentile	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
≥75th percentile	1.68 (1.68-1.69)	2.27 (2.26-2.28)	1.91 (1.90-1.92)	1.76 (1.74-1.77)
Years since graduation from medical school				
0-5	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
6-20	1.05 (1.04-1.06)	1.19 (1.16-1.22)	1.38 (1.34-1.41)	1.28 (1.22-1.33)
≥21	1.05 (1.04-1.06)	1.14 (1.12-1.16)	1.48 (1.44-1.51)	1.30 (1.24-1.36)
Geographic region				
Northeast	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Midwest	0.92 (0.91-0.92)	1.55 (1.54-1.56)	0.73 (0.72-0.73)	1.52 (1.50-1.55)
South	1.10 (1.10-1.11)	1.65 (1.64-1.66)	0.87 (0.86-0.87)	1.83 (1.81-1.86)
Pacific West	0.64 (0.64-0.64)	1.21 (1.20-1.22)	1.06 (1.05-1.06)	1.28 (1.26-1.31)
Mountain West	0.87 (0.86-0.87)	1.70 (1.68-1.72)	0.92 (0.91-0.93)	1.37 (1.34-1.41)
Population density				
Rural	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Urban	1.02 (1.01-1.02)	0.94 (0.94-0.95)	1.18 (1.17-1.19)	0.89 (0.88-0.90)
Median household income in zip code[d]	0.95 (0.95-0.95)	0.98 (0.98-0.98)	0.97 (0.97-0.98)	0.93 (0.92-0.93)
% Claims for low-income subsidy beneficiaries	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.99 (0.99-0.99)	1.00 (1.00-1.00)
% Claims for Medicare Advantage Part D beneficiaries	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.99 (0.99-1.00)	1.00 (1.00-1.00)

[a] Results shown are odds ratios (with 95% confidence intervals) of prescribing the target drug over alternatives within the drug class. All *P* values for coefficient estimates are <.001 except for 2 estimates (% claims for LIS beneficiaries for rosuvastatin [*P* = .14] and total volume of claims within the drug-class for desvenlafaxine [*P* = .38]).

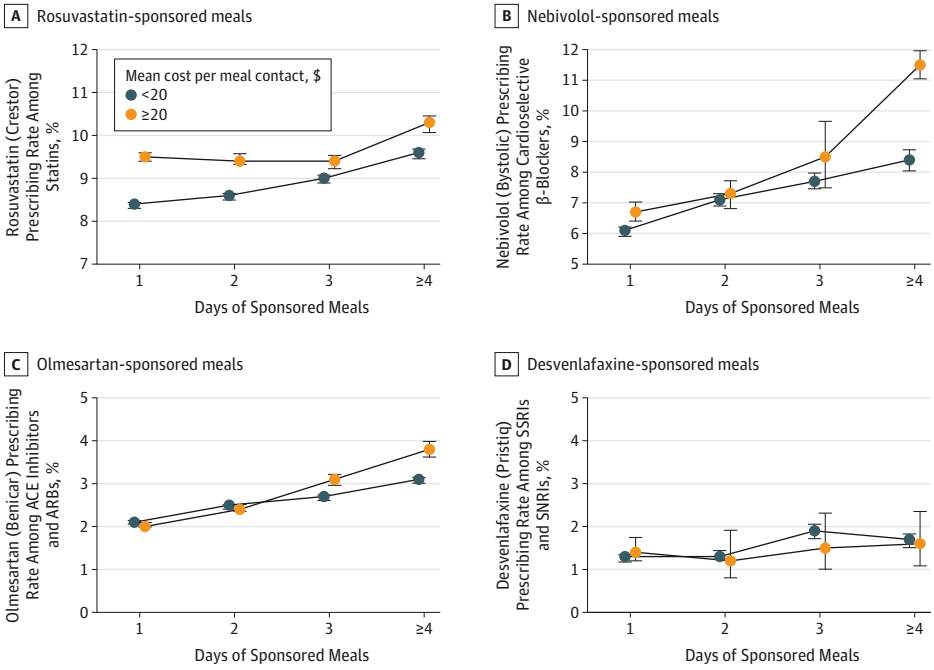
[b] Refers to the number of days between August 1 and December 31, 2013, in which the physician received at least 1 food or beverage payment promoting the target drug.

[c] Prescription volume was divided by 100 to produce more meaningful odds ratios.

[d] Median household income in zip code was converted to a z-score.

Figure 2 shows predicted probabilities for prescribing the target drug, according to mean cost per meal received. Receipt of costlier meals was significantly associated with increased target-drug prescribing for all drugs except desvenlafaxine, with ORs ranging from 1.02 to 1.13 (eTable 3 in the Supplement). The interaction between mean cost per meal and

Figure 2. Predicted Probabilities for Prescribing the Target Drug as a Percentage of All Prescriptions in the Class, According to the Number and Cost of Sponsored Meals Received by Each Physician



The figure shows predicted probabilities for prescribing the target drug over alternatives within the treatment class, based on the cost and number of meals received promoting the target drug. Predicted probabilities are calculated for physicians with the highest-frequency values of all characteristics in Table 1 (male sex, internal medicine specialty, Southern region, urban location, group size ≥51, ≥20 years since medical school graduation, and mean values for prescribing volume, income in zip code, and percentage of low-income subsidy and Medicare Advantage Part D patients). A, Statins. B, Cardioselective β-blockers. C, Angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers (ACE inhibitors and ARBs). D, Selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs). Error bars indicate 95% confidence intervals.

number of days receiving sponsored meals was also significant for all drugs except desvenlafaxine, but the interaction effects were too small to be qualitatively meaningful (data not shown).

In sensitivity analyses adjusted for propensity score decile (eTable 4 in the Supplement), receipt of meals related to target drugs was associated with increased odds of prescribing rosuvastatin (adjusted OR, 1.19; 95% CI, 1.19-1.20), nebivolol (OR, 1.79; 95% CI, 1.78-1.80), olmesartan (OR, 1.74; 95% CI, 1.73-1.75), and desvenlafaxine (OR, 2.30; 95% CI, 2.25-2.34). In falsification tests (eTable 5 in the Supplement), receiving a desvenlafaxine-related meal did not predict rosuvastatin prescribing (OR, 0.99; 95% CI, 0.98-1.00); receiving a rosuvastatin-related meal predicted desvenlafaxine prescribing, but with much smaller effect sizes than desvenlafaxine-related meals (OR, 1.22; 95% CI, 1.20-1.24 compared with OR, 2.18; 95% CI, 2.13-2.23 for desvenlafaxine-related meals).

Our findings were unchanged when study group inclusion criteria were increased from 20 to 200 prescriptions in the class (eTable 6 in the Supplement), when claims were standardized to 30-day supplies (eTable 7 in the Supplement), and in a sensitivity analysis of only high-intensity statins, with slightly smaller effect sizes (eTable 8 in the Supplement).

Other physician-level predictors of target-drug prescribing (Table 3) included high brand-name drug use across all medication classes, being in solo or small-group practice, graduating from medical school more than 5 years ago, practicing in the South, and being a psychiatrist (for desvenlafaxine) or a cardiologist (for rosuvastatin and nebivolol).

Discussion

We linked 2 national data sets to quantify the association between industry payments and physician prescribing patterns. We found that the receipt of industry-sponsored meals was associated with an increased rate of prescribing the brand-name medication that was being promoted.

As compared with the receipt of no industry-sponsored meals, we found that receipt of a single industry-sponsored meal, with a mean value of less than $20, was associated with prescription of the promoted brand-name drug at significantly higher rates to Medicare beneficiaries. The differences persisted after controlling for prescribing volume and potential confounders such as physician specialty, practice setting, and demographic characteristics. Furthermore, the relationship was dose dependent, with additional meals and costlier meals associated with greater increases in prescribing of the promoted drug. Our findings were consistent across 4 brand-name drugs, including rosuvastatin, the third-costliest drug in Medicare Part D ($2.2 billion in federal expenditures in 2013) after esomeprazole magnesium (Nexium) and fluticasone propionate/salmeterol (Advair Diskus).[33]

Our results are consistent with recent analyses that linked federal or state-level physician payment records with Medicare Part D prescribing data. These studies found that industry payments in general (rather than payments linked to a specific drug) were associated with an overall increase in the prescribing of brand-name drugs.[4,16,17] However, the analy-

ses did not link the promotion of specific drugs with prescribing rates for those drugs. A study of 2444 Massachusetts physicians found that for every $1000 received from industry (for any drug), a physician's brand-name statin prescribing rate increased by 0.1%.[16] In comparison, our study found a significant association between attending a single meal promoting a specific drug, with a mean value of less than $20, and the prescribing of the promoted drug over therapeutic alternatives.

Our findings are also consistent with smaller studies that relied on physician self-report or institution-level data.[10-13] In single-hospital studies, exposure to sponsored meals has been associated with increased clinic-wide use of the promoted drug,[15] choice of the promoted drug when presented with a clinical scenario,[34] and requests to add the promoted drug to the hospital formulary.[35] Marketing studies demonstrate that industry outreach to physicians facilitates the adoption of new drugs[36]; however, the content of these presentations is not actively monitored by the FDA. Industry-sponsored meals have been associated with learning inaccurate information about the sponsor's and competitor's drug[37] and with increased cost of prescribing.[38]

Our data are cross-sectional. The findings reflect an association, and not necessarily causality. Because we linked 5 months of Open Payments data with 1 year of Medicare Part D prescription data, we also could not determine whether high prescription rates for brand-name drugs were preceded, followed, or temporally unrelated to the receipt of industry-sponsored meals. The policy implications of our findings thus depend on further clarification of the mechanism of the association between the receipt of industry-sponsored meals and physician prescribing behavior. If events where industry-sponsored meals are provided affect prescribing by informing physicians about new evidence and clinical guidelines, then the receipt of sponsored meals may benefit patient care. If physicians, however, choose to attend industry events where information is provided about drugs they already prefer, then meals may have no affect on prescribing patterns. If, alternatively, meals change physicians' prescribing practices as a result of promotional influence, either by encouraging future use or rewarding an ongoing preference for the promoted drug, this would be cause for concern.

Our findings support the importance of ongoing transparency efforts in the United States and Europe.[1,3,5] Although voluntary guidelines from the Manufacturers of America allow meals and gifts to physicians of up to $100 in value,[39] our findings indicate that even payments of less than $20 are associated with different prescribing patterns. Small payments and meals should continue to be monitored in the United States and should be incorporated into the European pharmaceutical industry's recent transparency initiative, which requires drug companies to publicly report payments to physicians with the exception of food and drinks.[5]

Future research could compare industry-sponsored meals and other methods for disseminating drug information, such as academic detailing[40] and independent drug bulletins,[41] with respect to the cost and quality of prescribing. The methods used in this study could be applied to other payment types, to drugs with varying degrees of generic competition and cost-effectiveness, and to brand-name drugs that compete within the same class.

This study has several limitations. In addition to the cross-sectional design and timing of the data (5 months of payment data and 12 months of prescription data), unmeasured confounders may bias our results. The 5 months of Open Payments data may not be representative of a full year. The questions that we examined should be evaluated with alternative study designs and additional years of data. We linked data sets using physician name and location, which may have introduced inaccuracies despite exclusion of physicians with identical matching criteria. We did not measure the use of therapeutic alternatives from other drug classes, and our analysis did not differentiate between new indications and refills or adjust for physicians' patient panel size or case mix. However, case mix is unlikely to fully explain variability after controlling for physician- and panel-level characteristics. In addition, our sensitivity analysis of high-intensity statins, which was intended to make patient populations more homogenous between physicians, was consistent with our other findings.

Limitations of the Open Payments data include minimal prerelease vetting by physicians,[2] nonreported payments (including free drug samples and patient education materials), limited information about the accuracy of the data, and deidentified and disputed payments, which were excluded. The exemption of indirect payments with unidentifiable recipients (such as refreshments at large conferences) is a limitation but improves the precision of the database as a whole by restricting reported payments to those that can be accurately attributed.

Conclusions

The receipt of industry-sponsored meals was associated with an increased rate of prescribing the promoted brand-name medication relative to alternatives within the drug class. The findings represent an association, not a cause-and-effect relationship.

ARTICLE INFORMATION

Accepted for Publication: April 19, 2016.

Correction: This article was corrected on August 1, 2016, to remove a reference to an out-of-date guideline.

Published Online: June 20, 2016. doi:10.1001/jamainternmed.2016.2765.

Author Contributions: Ms DeJong and Mr Aguilar had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Ms DeJong and Mr Aguilar contributed equally to this article.
Study concept and design: DeJong, Aguilar, Tseng, Dudley.
Acquisition, analysis, or interpretation of data: DeJong, Aguilar, Lin, Boscardin, Dudley.
Drafting of the manuscript: DeJong, Aguilar.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Aguilar, Tseng, Boscardin.
Study supervision: Dudley.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was conducted with support from the National Center for Advancing Translational Sciences, National Institutes of Health (UCSF-CTSI grant TL1 TR000144 to Ms DeJong); and by the Hawaii Medical Service Association Endowed Chair in Health Services and Quality Research at the University of Hawaii (support for Dr Tseng).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study;

collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; or the decision to submit the manuscript for publication.

Disclaimer: This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Hawaii Medical Service Association Endowed Chair in Health Services and Quality Research.

REFERENCES

1. Open Payments. Baltimore, MD: Centers for Medicare & Medicaid Services; 2015. https://openpaymentsdata.cms.gov/dataset/General-Payment-Data-with-Identifying-Recipient-In/hrpy-hqv8. Accessed September 15, 2015.

2. Santhakumar S, Adashi EY. The Physician Payment Sunshine Act: testing the value of transparency. *JAMA*. 2015;313(1):23-24.

3. Groeger L, Ornstein C, Tigas M, Jones RG. Dollars for docs: how industry dollars reach your doctors. New York, NY: ProPublica; 2015. https://projects.propublica.org/docdollars/. Accessed September 20, 2015.

4. Ornstein C, Jones RG, Tigas M. Now there's proof: docs who get company cash tend to prescribe more brand-name meds. New York, NY: ProPublica. https://www.propublica.org/article/doctors-who-take-company-cash-tend-to-prescribe-more-brand-name-drugs. Published March 17, 2016. Accessed April 9, 2016.

5. European Federation of Pharmaceutical Industries and Associations (EFPIA). EFPIA Code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals and healthcare organisations. Brussels, Belgium: EFPIA; 2013. http://transparency.efpia.eu/the-efpia-code-2. Accessed April 13, 2016.

6. Rosenbaum L. Conflicts of interest: part 1: reconnecting the dots—reinterpreting industry-physician relations. *N Engl J Med*. 2015;372(19):1860-1864.

7. Greenberg SB, Vender JS. Point: should academic physicians lecture as members of industry speaker bureaus? yes. *Chest*. 2014;146(2):250-252.

8. Steinbrook R, Kassirer JP, Angell M. Justifying conflicts of interest in medical journals: a very bad idea. *BMJ*. 2015;350:h2942.

9. Brennan TA, Rothman DJ, Blank L, et al. Health industry practices that create conflicts of interest: a policy proposal for academic medical centers. *JAMA*. 2006;295(4):429-433.

10. Wazana A. Physicians and the pharmaceutical industry: is a gift ever just a gift? *JAMA*. 2000;283(3):373-380.

11. Lieb K, Scheurich A. Contact between doctors and the pharmaceutical industry, their perceptions, and the effects on prescribing habits. *PLoS One*. 2014;9(10):e110130.

12. Robertson C, Rose S, Kesselheim AS. Effect of financial relationships on the behaviors of health care professionals: a review of the evidence. *J Law Med Ethics*. 2012;40(3):452-466.

13. Spurling GK, Mansfield PR, Montgomery BD, et al. Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: a systematic review. *PLoS Med*. 2010;7(10):e1000352.

14. Windmeijer F, de Laat E, Douven R, Mot E. Pharmaceutical promotion and GP prescription behaviour. *Health Econ*. 2006;15(1):5-18.

15. Huang FY, Weiss DS, Fenimore PG, et al. The association of pharmaceutical company promotional spending with resident physician prescribing behavior. *Acad Psychiatry*. 2005;29(5):500-501.

16. Yeh JS, Franklin JM, Avorn J, Landon J, Kesselheim AS. Association of industry payments to physicians with the prescribing of brand-name statins in Massachusetts [published online May 9, 2016]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2016.1709.

17. Perlis RH, Perlis CS. Physician payments from industry are associated with greater Medicare Part D prescribing costs. *PLoS One*. 2016;11(5):e0155474.

18. Physician Compare. Baltimore, MD: Centers for Medicare & Medicaid Services; 2015. https://www.medicare.gov/physiciancompare/. Accessed September 25, 2015.

19. Medicare Provider Utilization and Payment Data: Part D Prescriber. Baltimore, MD: Centers for Medicare & Medicaid Services; 2015. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Part-D-Prescriber.html. Accessed September 10, 2015.

20. Donohue JM, Morden NE, Gellad WF, et al. Sources of regional variation in Medicare Part D drug spending. *N Engl J Med*. 2012;366(6):530-538.

21. Rizzo JA. Advertising and competition in the ethical pharmaceutical industry: the case of antihypertensive drugs. *J Law Econ*. 1999;42:89-116.

22. Shrank WH, Choudhry NK, Agnew-Blais J, et al. State generic substitution laws can lower drug outlays under Medicaid. *Health Aff (Millwood)*. 2010;29(7):1383-1390.

23. Kanavos P, Costa-Font J, Seeley E. Competition in off-patent drug markets: issues, regulation and evidence. *Econ Policy*. 2008;23:500-544.

24. Food and Drug Administration (FDA). *Orange Book: Approved Drug Products With Therapeutic Equivalence Evaluations*. Silver Spring, MD: FDA; 2015. http://www.accessdata.fda.gov/scripts/cder/ob/. Accessed September 27, 2015.

25. Laoutidis ZG, Kioulos KT. Desvenlafaxine for the acute treatment of depression: a systematic review and meta-analysis. *Pharmacopsychiatry*. 2015;48(6):187-199.

26. Green JB, Ross JS, Jackevicius CA, Shah ND, Krumholz HM. When choosing statin therapy: the case for generics. *JAMA Intern Med*. 2013;173(3):229-232.

27. FDA warning letter: Bystolic (nebivolol) tablets. Silver Spring, MD: Food and Drug Administration; 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm054010.pdf. Accessed October 4, 2015.

28. Matchar DB, McCrory DC, Orlando LA, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Ann Intern Med*. 2008;148(1):16-29.

29. VA National Formulary. Washington, DC: Department of Veterans Affairs; 2015. http://www.pbm.va.gov/nationalformulary.asp. Accessed October 10, 2015.

30. WWAMI Rural Health Research Center. Rural-Urban Commuting Area (RUCA) Data, version 2.0. http://depts.washington.edu/uwruca/ruca-data.php. Accessed September 27, 2015.

31. American fact finder. Washington, DC: Census Bureau. http://factfinder.census.gov/faces/nav/jsf/pages/index.xhtml. Accessed September 27, 2015.

32. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25)(suppl 2):S1-S45.

33. CMS releases prescriber-level Medicare data for first time. Baltimore, MD: Centers for Medicare & Medicaid Services; 2015. https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2015-Fact-sheets-items/2015-04-30.html. Accessed September 20, 2015.

34. Spingarn RW, Berlin JA, Strom BL. When pharmaceutical manufacturers' employees present grand rounds, what do residents remember? *Acad Med*. 1996;71(1):86-88.

35. Chren MM, Landefeld CS. Physicians' behavior and their interactions with drug companies: a controlled study of physicians who requested additions to a hospital drug formulary. *JAMA*. 1994;271(9):684-689.

36. Lublóy Á. Factors affecting the uptake of new medicines: a systematic literature review. *BMC Health Serv Res*. 2014;14:469.

37. Ziegler MG, Lew P, Singer BC. The accuracy of drug information from pharmaceutical sales representatives. *JAMA*. 1995;273(16):1296-1298.

38. Caudill TS, Johnson MS, Rich EC, McKinney WP. Physicians, pharmaceutical sales representatives, and the cost of prescribing. *Arch Fam Med*. 1996;5(4):201-206.

39. Pharmaceutical Research and Manufacturers of America (PhRMA). Code on interactions with health care professionals. Washington, DC: PhRMA; 2008. http://www.phrma.org/principles-guidelines/code-on-interactions-with-health-care-professionals. Accessed December 15, 2015.

40. O'Brien MA, Rogers S, Jamtvedt G, et al. Educational outreach visits: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev*. 2007;CD000409(4):CD000409.

41. Burnand B. Independent drug bulletins to promote the prescription of appropriate drugs: a necessary but difficult task. *Bull World Health Organ*. 2013;91(6):391-391A.